Polymyxin B-direct hemoperfusion therapy contributes to oxygen delivery in septic patients

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IL-6 and IFNγ play a role in fatal cases of 5N1 influenza in children

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Background: Fatal human critical cases associated with influenza A subtype H5N1 have been documented in Bandung, Indonesia. Of four children, three died. We determined the level of cytokines and chemokines in those patients.
Methods: The Luminex method was used to look for the profile of cytokine and chemokine gene expression induced by H5N1 influenza virus from patient's serum.
Results: We found that H5N1 influenza virus in the dead children was a more potent inducer of IL-6, the level being higher (17.00, 74.31, 85.75) than in the one child who survived (4.78). The IFNγ level of the fatal causes was also higher (21.43, 31.75, 384.38) than in the one child who recovered (5.51). This suggested that a cytokine storm may play a role in the pathogenesis of fatal H5N1 cases.
Conclusion: The H5N1 influenza A virus is a potent inducer of proinflammatory cytokines and chemokines. This hyperinduction of cytokines may be relevant to mortality of children with H5N1 infection.

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Abstract withdrawn

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Involvement of thrombopoietin in the development of organ injury in a mouse model of cecal ligation and puncture-induced sepsis

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Background: Sepsis-induced organ damage is a leading cause of death in critically ill patients. Thrombopoietin (TPO) is a humoral growth factor mainly involved in regulation of platelet number and function. High circulating levels of TPO are detectable in septic adults and children and are related to sepsis severity. We have previously shown a correlation between TPO levels and platelet activation in septic burned patients, where circulating activated platelets may cause microthrombotic events that lead to organ damage. Our aim was to evaluate the contribution of TPO in organ injury in a murine model of polymicrobial sepsis. To this end, we synthesized and used a chimeric fusion protein, named mouse TPO Receptor-Maltose Binding Protein (mTPOR-MBP), able to inhibit TPO biological activity.
Methods: Male C57BL/6 mice were randomized to cecal ligation and puncture-induced sepsis (CLP) or to laparotomy (sham) surgery. CLP mice received 40 μg mTPO-MBP or sterile saline 10 minutes after surgery. Immediately after and 6 hours after surgery all animals received 0.08 mg/kg buprenorfin in 1.5 ml sterile saline subcutaneously. After 18 hours blood was collected from the cava vein and used for cell count, flow cytometric analysis of leukocyte-platelet interaction and to obtain plasma. Plasma TPO levels were determined by ELISA. The lung and liver were excised and fixed in 4% paraformaldehyde solution. An expert pathologist blinded to experimental groups quantified organ damage.
Results: Plasma TPO levels were significantly higher in septic mice (nine mice in each group). Leukocyte and platelet counts did not significantly differ in the CLP group treated with mTPOR-MBP compared with the CLP control group. In contrast, the percentage of monocyte-platelet aggregates, a marker of platelet activation, was significantly reduced after treatment with mTPOR-MBP. Moreover, TPO blockade by mTPOR-MBP administration induced a significant reduction of histological alterations in the lung, as evaluated by neutrophil infiltration and thickening of the alveolar-capillary membrane, and liver tissue samples, as evaluated by the number of microabscesses.
Conclusion: Increased circulating levels of TPO during experimental sepsis may have a role in the development of organ damage. Inhibition of TPO biological activity may represent a novel promising therapeutic approach to prevent organ failure in severe sepsis.

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Cholecystokinin protects rats against *Staphylococcus aureus*-induced sepsis

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Background: Cholecystokinin (CCK) was firstly described as a gastrointestinal hormone, but immune cells express their receptors, suggesting a possible involvement of this peptide in pathophysiological processes. Our aims were to evaluate the role of CCK on resistance against Gram-positive *Staphylococcus aureus*-induced sepsis, as well as cell influx to infectious focus. Furthermore, since nitric oxide, TNFα and IL-10 play a key role in the innate immune system controlling bacterial infection, we also evaluated the synthesis of these inflammatory mediators during this sepsis model.
Methods: Male Wistar rats (180 to 200 g) received an intraperitoneal injection of proglumide (P) (nonselective CCK receptor antagonist; 30 or 50 mg/kg) 30 minutes before bacterial *S. aureus* inoculum (0.5 to 1 × 10^{10} CFU/animal). At 4 and 24 hours after sepsis induction, blood and peritoneal lavage fluid (PLF) were collected for microbiological analysis, cytokines and nitrate quantifications and also differential cell counting. Nitrate was detected by chemiluminescence, while TNFα and IL-10 were determined by ELISA sandwich kits.
Results: The pretreatment with P at higher dose (50 mg/kg) increased bacteremia in comparison with the saline-injected group (2,052 ± 810.7 vs. 154.3 ± 47.0 CFU/ml, $P < 0.01$) at 4 hours after sepsis induction. At the same time point, the bacterial counting in PLF increased in a dose-dependent manner in the P-treated rats ($P < 0.05$). On the other hand, only the higher P dose elevated significantly the CFU/ml in the PLF at 24 hours (97.75 ± 12.77 × 10^4 vs. 35 ± 10.05 × 10^4 CFU/ml, $P < 0.05$). The plasma TNFα and nitrate concentrations were not changed by treatment or time after sepsis induction. However, the administration of CCK receptors antagonist reduced the TNFα production in comparison with the control group in PLF, at both time points. The plasma IL-10 concentration increased at 4 hours in P-treated rats, while at 24 hours it was reduced (85.83 ± 48.0 vs. 1,698 ± 265.6 pg/ml, $P < 0.001$). In PLF, the rats pretreated with P reduced the IL-10 measurements ($P < 0.05$) when compared with the control group. In agreement, the macrophage influx to peritoneal infectious focus was compromised by treatment with a high P dose at 24 hours after *S. aureus*-induced sepsis (3,947.73 ± 269.99 vs. 5,629.61 ± 786.90 cells/μl; $P < 0.05$). Moreover, the neutrophil count did not change among the experimental groups (6,860.59 ± 211.90 vs. 6,273.54 ± 798.91 cells/μl).
Conclusion: These data suggest a protective role for CCK peptide during *S. aureus*-induced sepsis, modulating the systemic and local inflammatory response, as well as increasing the macrophage influx to the infectious focus.

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Polymyxin B-direct hemoperfusion therapy contributes to oxygen delivery in septic patients

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Background: Since 1994, Polymyxin B-direct hemoperfusion (PMX-DHP) (Toraymyxin®; Toray Medical Co., Tokyo, Japan) has been approved as

a therapy for patients with severe sepsis or septic shock due to Gram-negative infection in Japan. However, its efficacy and indication are still controversial issues. Recently, randomized controlled studies are ongoing in other countries. Our hypothesis is that PMX-DHP therapy may improve the hemodynamic status in septic patients.
Methods: From July 1994 to June 2010, all adult patients treated with PMX-DHP and receiving a pulmonary arterial catheter (PAC) in our ICU were included in this retrospective observational study. Patients' clinical, microbiological and PAC data were collected from medical archives. PAC variables were compared between immediately before and immediately after PMX-DHP therapy. Values were expressed as mean ± SD. Data were analyzed by Wilcoxon signed-ranks test, chi-square test and Fisher's exact probability test. $P < 0.05$ was considered statistically significant.
Results: Sixty-three patients (36 men, 27 women; age range 24 to 89 years (mean 63.4 ± 14.8)) were studied. The mortality rate was 30.2% at 28 days after PMX-DHP. The APACHE II score and SOFA score on the day of PMX-DHP therapy were 20.2 ± 14.8 and 7.3 ± 3.8, respectively. Mean arterial pressure (MAP; mmHg), cardiac index (CI; l/minute/m^2), and oxygen delivery and consumption (DO_2 and VO_2; ml/minute) significantly improved after PMX-DHP therapy (77.5 ± 22.5 vs. 84.1 ± 23.4, $P = 0.0013$; 3.9 ± 1.5 vs. 4.3 ± 1.2, $P = 0.0006$; 951.6 ± 403.5 vs. 1,002.5 ± 394.0, $P = 0.013$; 233.5 ± 80.6 vs. 248.0 ± 84.1, $P = 0.004$, respectively). The systemic venous resistance index (SVRI) (dyn second m^2/cm^5) and mixed venous oxygen saturation (SvO_2; %) were not statistically different before and after PMX-DHP therapy (1,573.6 ± 614.6 vs. 1,527.7 ± 575.5, $P = 0.069$; 71.9 ± 9.0 vs. 74.1 ± 7.5, $P = 0.082$). The inotropic score and P/F ratio improved after the therapy (9.9 ± 15.9 vs. 7.5 ± 12.5, $P = 0.018$; 269.8 ± 108.5 vs. 300.6 ± 133.4, $P = 0.003$).
Conclusion: MAP, CI, DO_2, VO_2, inotropic score and P/F ratio improved after PMX-DHP therapy, while SVRI and SVO_2 did not change. PMX-DHP could contribute to oxygen delivery due to improve hemodynamic status, while decreasing inotropic agents in septic patients.

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Sepsis in neonates: experience in a tertiary-care hospital

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Background: Sepsis is a common condition in newborns, which has significant morbidity and mortality worldwide. In recent years, multiple factors have led to an increase in its incidence, such as the use of invasive diagnostic procedures, broad-spectrum antimicrobial therapy and an increase of immunocompromised patients. There have also been changes in the profile of the agents causing sepsis. The aims of this study were the determination of the annual incidence of neonatal sepsis (early-onset and late-onset), analyzing their clinical course, significant microorganisms isolated and the profile of antimicrobial resistance.
Methods: One hundred and ninety-eight cases of sepsis were studied, collected over the past five years (2007 to 2011). Early-onset neonatal sepsis was defined as that which appeared before 3 days of life and late-onset neonatal sepsis if it happened later. Blood cultures were incubated in the BACTEC FX System (Becton Dickinson), and identification and antimicrobial susceptibility testing were done by the Wider system (Soria Melguizo). Yeasts were identified by ID32C (bioMerieux).
Results: Of the 198 detected sepsis cases, 173 (87.4%) were late and 25 (12.6%) were early. While the annual incidence rate of early-onset sepsis was uniform in each year, the late-onset sepsis has experienced an increase in 2011. The mortality rate was similar throughout the study (10.8%). Gram-negative bacilli are the most frequently isolated (48%), with predominance of enterobacteria compared with nonfermenters (84 vs. 11 cases), followed by Gram-positive cocci (36%) and yeast (16%). In candidemia most common are nonalbicans species of *Candida* (27 vs. 5 cases), with *Candida parapsilosis* more frequently isolated (65.6%). *Klebsiella pneumoniae* (33 strains) was the more frequent microorganism, followed by *Escherichia coli*, *Staphylococcus epidermidis*, *C. parapsilosis* and *Enterobacter cloacae*. With respect to antibiotic resistance, 11.1% of *Staphylococcus aureus* were MRSA and 19% (16 strains) of enterobacteria were ESBL producing. Only one strain of *Pseudomonas aeruginosa* was resistant to imipenem by metallobetalactamases.
Conclusion: *K. pneumoniae* was the organism responsible for more episodes of sepsis in neonates. As in other studies in neonatology, this study highlights the prevalence of nonalbicans species in candidemia due to the frequency of *C. parapsilosis*. Late-onset sepsis has increased by Gram-negative bacilli in the last year, probably due to the occurrence of a nosocomial outbreak of ESBL-producing *E. cloacae*. However, the mortality rate from sepsis has remained stable. When clinically evaluated, cases of sepsis can be detected as a predominance of enterobacteria against *S. epidermidis*, highlighting the importance of careful analysis of clinical outcomes.

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Is urinary kidney injury molecule-1 a good marker for acute kidney injury in septic shock?

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Background: Kidney injury molecule-1 (KIM-1) is a new biomarker promising a better detection and diagnostic quality of acute kidney injury (AKI).
Methods: This clinical prospective study - approved by the local ethics committee - was performed to assess urinary levels of KIM-1 by ELISA technique in 38 patients with septic shock (Table 1). They were prospectively enrolled within 24 hours of onset of signs of infection, if they met the criteria for septic shock as defined by the members of the ACCP/SCCM Consensus Conference Committee. KIM-1 levels were quantified on admission (baseline, day 0) and on days 4, 7 and 10 of the ICU stay. The patients were classified by AKIN and RIFLE criteria. Data were analyzed with regard to the prognostic value of survival, need for renal replacement therapy (RRT) and correlation with renal function parameters (plasmatic urea and creatinine, creatinine elimination and clearance, free water clearance, fractional sodium excretion) or hepatic laboratory findings (albumin, total bilirubin, ASAT, ALAT, γ-GT). Data are given as mean ± SEM.
Results: The urinary KIM-1 concentration on admission showed no significant difference with respect to survival of patients. However, the urinary KIM-1 concentration determined on days 4, 7 and 10 was higher in patients surviving septic shock ($P < 0.001$ on days 4 and 7). Elimination displayed lower levels in deceased patients ($P < 0.05$ on days 0 and 4), whereas urinary output was higher in survivors during the whole ICU stay ($P < 0.05$ on day 7). Urinary KIM-1 concentration did not differ between AKIN and RIFLE classification groups. Urinary KIM-1 elimination per 24 hours on days 0, 4 and 7 was higher in stage 1 than in stage 2 or 3 of the AKIN classification, respectively (both $P < 0.05$). If patients were classified by RIFLE criteria, urinary KIM-1 elimination was also higher in the risk group as compared with the injury or failure group without reaching significance. However, the need for RRT was reflected by a higher urinary KIM-1 concentration after admission ($P < 0.05$ on days 4 and 10), a lower KIM-1 elimination and urinary output during the whole ICU stay (KIM-1 elimination:

Table 1(abstract P59) Demographic data

Age (years)	57.2 ± 2.6
Gender (male/female)	27/11
BMI (kg/m^2)	29.7 ± 1.5
Length of ICU stay (days)	19.5 ± 2.7
Mortality (%)	13.2 (5 out of 38 patients)
SAPS score	63.4 ± 2.7
APACHE II score	28.8 ± 1.3
SOFA score	12.7 ± 0.5
MOD score	10.4 ± 0.6
RIFLE (number per group)	no AKI = 28; risk = 4; injury = 3; failure = 3;
AKIN (number per group)	no AKI = 25; stage 1 = 1; stage 2 = 1; stage 3 = 11
Need for RRT (yes/no)	16/22